REMARKS

Claims 1-3, 5-8, 16-18, 21-23 are pending for purposes of the instant Office Action.

Applicants acknowledge and appreciate the withdrawal of the rejection under 35 U.S.C. § 112, first paragraph concerning new matter in view of the amendment previously submitted.

Enablement Rejection

Claims 1 to 3, 5 to 8, 16 to 18, and 21 to 23 were rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement for a method for diagnosing GPC3 protein expressing cancer, including hepatic cancer.

The Examiner specifically argued that other than for melanoma "one cannot predict the claimed method would be successful in detecting the presence of any cancer that overexpresses GPC3, including hepatic cancer, when based on an increase in the level of GPC3 in blood, serum or plasma as compared to that of healthy individuals". The Examiner asserted two reasons:

1) According to the Examiner the claimed method is non-specific for hepatic cancer, and cannot distinguish suspected hepatic cancer from liver cirrhosis, because the level of soluble GPC3 in blood or serum or plasma is increased in both hepatic cancer patients and liver cirrhosis as compared to soluble GPC3 in blood or serum or plasma of healthy individual, in view of the teaching of Hippo et al, of record.

2) According to the Examiner other than a single cancer, melanoma, that can be detected with the claimed method, one cannot predict there exist any other cancers that overexpress the protein GPC3 in blood,serum or plasma. The Examiner specifically contends that one cannot predict whether cancers

> such as lung cancer, colon cancer, mammary cancer, prostate cancer and lymphomas overexpress the protein GPC3 in blood, serum or plasma, when based solely on the data from cancer cell lines in culture, due to the well known cell culture artifacts, in view of the teaching of Drexler et al, Tian et al, Van Dyke et al and Kunkel et al.

In response to the Examiner's first reason, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 of Professor Hiroyuki Aburatani. Applicants note that Professor Aburatani is one of the inventors of the present application.

In the Declaration, Professor Aburatani maintains that 100% accuracy is not required, or expected, for any cancer markers. (Aburatani Declaration at paragraph 9) According to Professor Aburatani, "those skilled in the art well recognize that existent traditional cancer markers provide false positives and that cancer markers used for diagnosing cancer frequently show positive values in benign disease. (Aburatani Declaration at paragraph 9) As stated by Professor Aburatani:

> As no cancer markers show 100% specificity (at least none of which I am aware), physicians, by necessity, understand how to make diagnostic decisions while keeping in mind the nature of a specific tumor marker. (Aburatani Declaration at paragraph 9)

Professor Aburatani supports this opinion by citing to the widely used cancer marker AFP which is used as a cancer marker for hepatocellular carcinoma ("HCC") but is known to show positive values in Liver Cirrhosis ("LC") or hepatitis. (Aburatani Declaration at paragraph 10) Professor Aburatani also explains that the Hippo et al. reference, which is of record, shows ROC (receiver-operating characteristic) curve analysis of sGPC3 and AFP in Figure D. (Aburatani Declaration at paragraph 10) As pointed out by Professor Aburatani:

> When 43 cases treated with surgery were confined to 32 cases with relatively early stage HCC (7 cases with WD HCC and 25 cases with MD HCC), the calculated area under the ROC curve for sGPC3 and AFP were 0.726 and 0.710, respectively,

> indicating that sGPC3 is superior to AFP (Figure 3D). The sensitivity of sGPC3 and AFP for the diagnosis of WD HCC and MD HCC was 50% and 47% respectively. Moreover, combination measurement of both markers in WD HCC and MD HCC also markedly improved sensitivity to 72%. These results clearly demonstrate the utility of sGPC3 as a cancer marker for HCC. (Aburatani Declaration at paragraph 10)

According to Professor Aburatani, further support for his position that 100% accuracy is not required for any cancer markers is found in the articles attached to his Declaration as Exhibit Nos. 7-15. (Aburatani Declaration at paragraph 11.) As demonstrated in the references set forth in Exhibits 7-10, even widely-used tumor markers often provide false positives and physicians understand that these markers sometimes show false positives but are still useful in diagnosis of cancer. (Aburatani Declaration at paragraph 11) For example, it can be seen in Exhibit 7 that AFP, a traditional HCC marker, shows a false positive in liver cirrhosis cases (see Exhibit 7, Figs. 1 and 2) and that a new marker AFP-L3, with alleged improved performance, still shows false positives. (Aburatani Declaration at paragraph 11.) Similarly, Exhibit 8 demonstrates that AFP can show a false positive in liver cirrhosis cases (see Exhibit 8 at Fig. 2, Table 3). (Aburatani Declaration at paragraph 11.) In Exhibits 9 and 10, PSA, a traditional tumor marker, is shown to give false positives (see Exhibit 9 at Figs. 1 and 2 and Exhibit 10 at p. 154, right column, lower paragraph). (Aburatani Declaration at paragraph 11.)

Furthermore, and as seen from the references in Exhibits 11-15 and Professor Aburatani's discussion of these references, those of skill in the art when using widely-used tumor markers known to often provide a false positive, know how to select a cut-off point to obtain a desirable combination of specificity and sensitivity. (Aburatani Declaration at paragraph 12).

For example, in Exhibit 11, the specificity and sensitivity of PSA are shown in Figure 1 to demonstrate a trade-off relationship with each other. (Aburatani Declaration at paragraph 13) Exhibit 11 teaches that one of skill in the art is able to select an appropriate cut-off level to obtain desirable specificity and sensitivity. (Aburatani Declaration at paragraph 13) It is

of note that Exhibit 11 was published in 2001 just after the priority date of the present application and therefore shows the state of the art as of the priority date.

Exhibit 12 shows that false positives for the marker CA 242 are found in normal subjects and in a benign disorder and that an average +/-2 standard deviation of normal subjects or 95 percentile of normal subjects can be used as a criterion value. (See, e.g. Exhibit 12, p. 217, left column, Fig 2). (Aburatani Declaration at paragraph 14)

Exhibit 13 again teaches that the cut-off levels for several tumor markers may be set in view of the balance of specificity and sensitivity. (See Exhibit 13, Table 1, and discussion of the same). (Aburatani Declaration at paragraph 15)

In Exhibit 14, specificity was examined under different cut-off points (see Exhibit 14, Table II) with the distribution of tumor and benign disorder demonstrating the existence of false positives (Exhibit 14, Fig 1). (Aburatani Declaration at paragraph 16) Exhibit 14 also teaches setting the cut-off value via the 95%-specificity approach (Exhibit 14, Table III). (Aburatani Declaration at paragraph 16)

Exhibit 15 teaches setting the cut off value of the marker based on the ROC curve (see Exhibit 15 at p. 2921, left column). (Aburatani Declaration at paragraph 17) Exhibit 15 explicitly states that "[n]one of these tests has 100% accuracy" (see Exhibit 15, p. 2921, left column, last paragraph). (Aburatani Declaration at paragraph 17)

In view of the teachings of these references, Professor Aburatani concludes that:

> Therefore, one of skill in the art, based on the evidence of Exhibits 11-15 clearly would be able to practice the claimed invention even if the method does not provide 100% specificity. In fact, those skilled in the art would recognize it unreasonable to require 100 % specificity to meet the enablement requirement in any type of diagnostic methods. (Aburatani Declaration at paragraph 18)

In response to the Examiner's second reason for rejection, Applicants again refer to the Professor Aburatani's Declaration under 37 C.F.R. § 1.132.

As explained by Professor Aburatani, Exhibits 1-6 show the expression of Gypican 3 in other types of cancer, including gastric carcinoma, thyroid cancer, chromophobe renal cell carcinoma, clear cell adenocarcinoma of ovary, lung squamous cell coarcinoma and germ cell tumors or ovary and testis. (Aburatani Declaration at paragraph 19). These articles clearly demonstrate that the present invention is also enabled with respect to cancers other than melanoma.

In view of the foregoing, it is respectfully submitted that the subject claims are enabling, and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Leslye Davidson
Reg. No. 38,854

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940